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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,816	09/01/2006	Makoto Asashima	P28509	1458

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EXAMINER	
ARIANI, KADE	
ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/549,816	ASASHIMA ET AL.	
	Examiner	Art Unit	
	KADE ARIANI	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☒ Claim(s) *1, 4-6, and 10-16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/02/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-16 are pending in this application and were examined on their merits.

Claim Objection

Claims 1, 4, 5, 6, and 10-16 are objected to because of the following informalities:

The word “tissue” in the recitation “an organ and/or tissue” in claims 1, 5, 6, 10-16 has to be preceded by the function word "a".

In claim 4 word “tissue” has to be preceded by function word “the”.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for “a method for forming cardiac muscle-like cell aggregates, smooth muscle cell-like aggregates, adipocytes, and an intestine-like structure from undifferentiated cells” derived from a vertebrate animal *in vitro,* which comprises the step of culturing the undifferentiated cells in the presence of Am80, PA024 and activin”, does not reasonably provide enablement for “a method for forming

an organ, wherein the organ formed is a heart, a smooth muscle tissue, a pancreas, and an adipocyte tissue in the presence of any retinoic acid X receptor agonist or antagonist". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described by the court *in In re Wands*, 8 USPQd 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of forming an organ and/or tissue from undifferentiated cells. The invention is in a class of invention, which CAFC has characterized as "the unpredictable arts such as chemistry and biology." Micogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed Cir. 2001).

The breadth of the claims

The claims broadly encompass a method for forming an organ from undifferentiated cells derived from a vertebrate animal *in vitro*, by culturing the undifferentiated cells in the presence of any retinoic acid X receptor antagonist or agonist.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there are a significant number retinoic acid X receptor (RXR) agonist and antagonist need to be examined. It would require significant amount of time to study RXR agonist and antagonist. This would require years of inventive effort, with each of the many inventing steps, not providing any guarantee of success in the succeeding steps.

Minucci et al. (Molecular & Cellular Biology, 1997, Vol. 17, No.2, p.644-655) teach "The presence of multiple retinoids that are differentially distributed in various tissues and differentially bind to RARs (retinoic acid receptors) and RXRs (retinoic acid X receptors) suggests that retinoid-dependent gene regulation and its biological effects are highly complex" (see p.644 1st column).

The unpredictability of the art and the state of the prior art

The art is unpredictable and complex with regard to RXR ligands. Minucci et al. further teach "Ligand binding and transcriptional activity of RXR may raise additional issues, as RXR forms heterodimers with several other nuclear receptors that respond to nonretinoid ligands" (see p.644 1st column).

Negative teachings in the art

Drysdale et al. (Developmental Biology, Vol. 188, p.205-215) teach "our results strongly suggest that exogenous retinoic acid (RA) blocks expression of myocardial differentiation markers. In general, and not just the expression of a subset of myocardial genes. In addition, late stage embryos fail to exhibit any detectable heart beat, indicating a failure to form the contractile apparatus" (p.211, 2nd column, 3rd paragraph).

Working examples

In the specification, the working examples are drawn to a method for forming cardiac muscle-like cell aggregates, smooth muscle cell-like aggregates, adipocytes, and an intestine-like structure from undifferentiated cells derived from a vertebrate animal *in vitro* by culturing the undifferentiated cells in the presence of Am80, PA024 and activin.

Guidance in the Specification

The specification does teach how to use this method for any agonist and antagonist of RXR receptor.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided

in the specification, the presence of only three working examples and the negative teachings of the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written and the instant application does not support the breadth of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "that does not substantially bind to the retinoic acid receptor subtype γ" in claim 7 is indefinite because from the way it is written it is confusing and it is not clear, which molecule does not bind to retinoic acid receptor subtype γ, the ligand or activin.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5-7, 9, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Moriya et al. (Develop. Growth Differ. , 2000, Vol. 42, p.593-602).

Claims 1, 2, 5-7, 9, and 12 are drawn to a method for forming an organ and/or tissue from undifferentiated cells derived from a vertebrate animal *in vitro*, which comprises the step of culturing the undifferentiated cells derived from a vertebrate animal in the presence of a retinoic acid X receptor (RXR) ligand, wherein the RXR ligand is a RXR agonist or antagonist, an organ or a tissue, a differentiation inducer which comprises a RXR ligand, and activin.

Moriya et al. disclose a method for *in vitro* pancreas formation from *Xenopus* ectoderm (undifferentiated cells derived from a vertebrate animal), culturing the undifferentiated cells derived from a vertebrate animal in the presence of all-trans-retinoic acid (please note that all-trans-retinoic acid is a RXR subtype-α ligand) and activin, an organ or a tissue, a differentiation inducer which comprises a RXR ligand (see abstract and p.594, 1st column 2nd and 3rd paragraphs, p. 595 2nd column and lines 15-18).

Moriya et al. therefore clearly anticipate the claimed invention.

Claims 1, 2, 3, 6, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Takahashi et al. (Journal of Medicinal Chemistry, August 2002, Vol. 45, No. 16, p.3327-3330).

Claims 1, 2, 3, 6, and 9 are drawn to a method for forming a tissue from undifferentiated cells derived from a vertebrate animal *in vitro*, which comprises the step of culturing the undifferentiated cells derived from a vertebrate animal in the presence of

a retinoic acid X receptor (RXR) ligand, wherein the RXR ligand is a RXR agonist or antagonist, a differentiation inducer for forming a tissue from undifferentiated cells which comprises a retinoic acid X receptor ligand, that does not substantially bind to the retinoic acid receptor subtype γ.

Takahashi et al. disclose a method which comprises the step of culturing undifferentiated cells derived from a vertebrate animal (HL-60 undifferentiated human promyelocytic leukemia cells) *in vitro* in the presence of retinoic acid X receptor (RXR) ligand, RXR agonist and antagonist, and differentiation-inducer Am80 (an RAR agonist that does not substantially bind to the RAR subtype γ)(Abstract. p.3328 Chart 1., p.3329 1st column 2nd paragraph, lines 10-17).

It has been noted that Takahashi et al. do not disclose a method for forming an organ and/or a tissue (pancreas). However, the differentiation inducer disclosed by Takahashi et al. is the same as the claimed inducer therefore it must have the same organ/tissue forming effects.

Takahashi et al. therefore clearly anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moriya et al. (Develop. Growth Differ. , 2000, Vol. 42, p.593-602) in view of Takahashi et al. (Journal of Medicinal Chemistry, August 2002, Vol. 45, No. 16, p.3327-3330) and further in view of Drysdale et al. (Developmental Biology, 1997, Vol. 188, p.205-215) and further in view of Neuville et al. (Arterioscler. Thromb. Vasc. Biol., 1999, Vol. 19, p.1430-1436).

Claims 1-16 are drawn to a method for forming an organ and/or tissue from undifferentiated cells derived from a vertebrate animal *in vitro*, which comprises the step of culturing the undifferentiated cells derived from a vertebrate animal in the presence of a retinoic acid X receptor (RXR) ligand, wherein the RXR ligand is a RXR agonist or antagonist, an organ or a tissue, a differentiation inducer which comprises a RXR ligand, and activin.

As mentioned immediately above Moriya et al. teach the limitations of claims 1, 2, 5-7, 9, and 12.

Moriya et al. do not teach the RXR ligand is 2- [N-cyclopropylmethyl-N- (5,6,7,8-tetrahydro" 5,5,8,8-tetramethylnaphthalen-2- yl)amino]pyrimidine'5carboxylic acid (PA024), and the RAR ligand is 4-[(5, 6, 7, 8,-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl] benzoic acid (Am80). However, Takahashi et al. teach RXR selective ligands PA024, and RAR selective agonist and a differentiation-inducer Am80 (Abstract, Introduction 1st column, p.3328 2nd column lines 1-2, p.3328 Chart 1.).

Takahashi et al. further teach “RXRs key role is in heterodimer formation with various nuclear receptors, including RARs and peroxisome proliferator-activated receptors (PPARs)”, and teach, antidiabetic and antiobesity activities of diazepine

derivatives which are RXR antagonists and can inhibit RXR heterodimers (p.3327 2nd column 1st paragraph).

Moreover, at the time the invention was made the effects of retinoic acid in cardiac differentiation (see Drysdale et al. Abstract and the entire document) and the role of RA-signaling and RXR ligands in the differentiation of smooth muscle cells (Neuville et al. see Abstract and Introduction) were documented and well known in the art.

Therefore, in view of the above teachings it would have been obvious to one of ordinary skill in the art to modify the method as taught by Moriya et al. by substituting the RXR and RAR ligands with ligands of Takahashi et al. in order to provide a method for forming a organ/tissue form undifferentiated cells derived from a vertebrate animal *in vitro*. The motivation as taught by Takahashi et al. would be to develop potent and selective RXR antagonists with clinical potential as antidiabetic and antiobesity agent and to devise new therapeutic strategies against the incurable disease diabetes.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kade Ariani whose telephone number is (571) 272-6083. The examiner can normally be reached on 9:00 am to 5:30 pm EST Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford Jr/
Primary Examiner, Art Unit 1651

Kade Ariani
Examiner
Art Unit 1651